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Special Article- Unusual Bleeding

Effect of Red Blood Cell Transfusion on Central Venous-to-Arterial Carbon Dioxide Difference in Anemic Surgical Patients – A Pilot Study

Anton Alpatov[1]; Maria Wittmann[1]; Heidi Ehrentraut[1]; Achilles Delis[1]; Jochen Hoch[2]; Andreas C Strauss[3]; Holger Bogatsch[4]; Patrick Meybohm[5]; Markus Velten[1#]; Tobias Hilbert[1#*]

[1]Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany
[2]Institute for Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Bonn, Germany
[3]Department of Orthopedics and Trauma Surgery, University Hospital Bonn, Bonn, Germany
[4]Clinical Trial Centre Leipzig, Leipzig, Germany
[5]University Hospital Würzburg, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Würzburg, Germany

***Corresponding author: Tobias Hilbert**
Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
Email: thilbert@uni-bonn.de

[#]These authors have contributed equally to this article.

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Abstract

Background: Biochemical markers for monitoring adequacy of cardiac output and tissue perfusion such as blood lactate and central venous oxygen saturation ($S_{cv}O_2$) are meanwhile well established in clinical routine. In addition, in recent years, the central venous-to-arterial carbon dioxide difference (dCO_2) has been evaluated as a further marker, and studies meanwhile have demonstrated the validity of an increased dCO_2 to identify capillary perfusion mismatches. However, results from animal studies suggest that dCO_2 may be influenced by altered hemoglobin values during severe bleeding. It was the aim of our study to evaluate if dCO_2 changes upon Red Blood Cell (RBC) transfusion in humans.

Methods: Patients of the ongoing LIBERAL trial were prospectively evaluated. Participants were aged ≥70 years and scheduled for elective intermediate or high risk orthopedic or trauma surgery with the clinical need for invasive blood pressure monitoring and central venous catheterization. During surgery, drop of hemoglobin triggered administration of one single RBC unit, together with arterial and central venous blood analysis immediately before as well as after transfusion.

Results: In total, 46 patients were analyzed. Baseline median hemoglobin before RBC transfusion was 8.35 (7.48–8.73)g/dl, while dCO_2 was 6.2 (3.4–9.6)mmHg. According to Spearman correlation, there was a linear association between pre-transfusion dCO_2 and $S_{cv}O_2$. Transfusion of one RBC unit resulted in a significant increase of median hemoglobin by 1.2 (0.7–1.63)g/dl ($p<0.0001$), and hemoglobin increase was more pronounced when pre-transfusion hemoglobin was low, as evidenced by a significant negative association between both parameters ($r=-0.61$, $p<0.0001$). Neither lactate nor $S_{cv}O_2$ nor dCO_2 were significantly influenced by transfusion. When the whole cohort was divided according to pre-transfusion dCO_2 levels using a cut-off value of 6 mmHg, median dCO_2 decreased significantly more pronounced following RBC transfusion when pre-transfusion values were high (>6 mmHg), compared to those patients with a pre-transfusion dCO_2 below 6 mmHg.

Conclusions: The results of our study suggest that crude dCO_2 is not influenced by moderate hemoglobin increases in orthopedic and trauma surgery patients. However, including dCO_2 into the decision whether to administer RBC or not may be an interesting reasonable approach for further investigations on the way towards more individualized transfusion regimens.

Keywords: Transfusion; Bleeding; Capillary perfusion; Microcirculation; Cardiac output; Central venous oxygen saturation

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Background

The purpose of hemodynamic optimization is to maintain adequate tissue perfusion. During capillary perfusion, oxygen is delivered to organs and tissues, while Carbon Dioxide (CO_2) produced during cell metabolism is washed out. Impaired microcirculation disrupts this exchange with the risk of tissue loss and organ death due to a critical mismatch between oxygen demand and delivery.

It is meanwhile recognized that basic and also advanced monitoring solely taking systemic hemodynamic variables (e.g., arterial blood pressure, cardiac output, global volume status) into account may only poorly reflect actual tissue perfusion [1,2]. Administration of inotropics, vasopressors and fluids in reaction to hypotension or cardiac output failure irrespective of knowing actual capillary perfusion may further worsen the situation. This concept of dissociation of micro- and macrocirculation is called the loss of hemodynamic coherence, reflecting that optimizing systemic surrogate variables does not necessarily result in restored microcirculation but sometimes rather leads to the opposite [2-4]. Therefore, ways to assess capillary perfusion and tissue oxygenation to guide hemodynamic optimization are mandatory.

In addition to technically more advanced approaches such as side stream dark field imaging or intravital tissue oxygen assessment electrodes that are complex and therefore only available in limited form [4], biochemical markers for monitoring adequacy of cardiac output and tissue perfusion are well established in clinical routine. As such, lactate and mixed (or central) venous oxygen saturation ($SmvO_2$ and $ScvO_2$) have become widely used as easily assessable parameters to validly guide fluid and catecholamine support and transfusion in critical situations such as bleeding, sepsis or cardiogenic shock [5]. In addition to that, in recent years, the central venous-to-arterial carbon dioxide difference (dCO_2) has been introduced and evaluated as a further marker for capillary perfusion mismatches. CO_2 produced during cell metabolism is either combined with water to form bicarbonate, bound to hemoglobin or physically dissolved in blood. As these, it is carried from the capillary bed via venules and larger veins to the pulmonary alveolar system for exhalation. As the principle of Fick not only applies for mixed venous oxygen saturation but also for dCO_2, CO_2 production is proportional to cardiac output and capillary perfusion, and therefore so is the difference between CO_2 partial pressure on the arterial and the one on the venous side. Studies meanwhile have demonstrated the validity of an increased dCO_2 to identify capillary perfusion mismatches, even when $ScvO_2$ is normal [6,7]. In critically ill patients, a cut-off value of 6 mmHg has been suggested to reflect the adequacy of tissue perfusion [8]. However, dCO_2 should be interpreted with caution in case of, e.g., respiratory alkalosis [9]. Moreover, results from animal studies suggest that dCO_2 may be influenced by altered hemoglobin values during severe bleeding [10]. Therefore, it was the aim of our study to evaluate if dCO_2 changes upon Red Blood Cell (RBC) transfusion in humans. Orthopedic and trauma surgery patients with both arterial and central venous catheters and clinical indication for RBC transfusion were evaluated.

Methods

The present study recruited consecutive patients from orthopedic or trauma surgery as part of a subgroup of the ongoing LIBERAL trial during August 2019 to January 2023. The LIBERAL trial is a prospective multicenter, randomized, open phase IV trial, investigating the effects of a liberal transfusion strategy of RBCs on mortality and anemia-associated ischemic events in elderly patients undergoing non-cardiac surgery. It is funded by the German Research Foundation (DFG, protocol no. ME 3559/3-1). For a detailed description of the protocol of the LIBERAL trial, see Meybohm et al [11]. All analyses were performed in accordance with the Declaration of Helsinki. The leading ethics committee (University Wuerzburg 87/17_ff) and local ethics committee (University Hospital Bonn, Germany; protocol number 096/17-AMG) considered the study (clinical trials: NCT03369210) to be compliant with the applicable professional codes and regulations and thereby approved the study protocol. Written informed consent was obtained from all included patients. In brief, patients aged ≥70 years and scheduled for elective intermediate or high risk orthopedic or trauma surgery with the clinically indicated need for invasive blood pressure monitoring and central venous catheterization were included.

Exclusion criteria comprised emergency surgery, refusal or inability to provide written informed consent, preoperative severe anemia with hemoglobin levels below 9.0g/dl, chronic kidney injury requiring dialysis, participation in other interventional trials, and preoperative autologous blood donation. Arterial as well as central venous catheterizations were performed by the attending anesthetist who was not part of the study personnel.

Hemoglobin levels were monitored during surgery. If they dropped below ≤9.0g/dl, patients were randomized either to a liberal (receiving one single RBC unit each time hemoglobin reaches ≤9.0g/dl) or restrictive transfusion regime (a single RBC unit each time hemoglobin reaches ≤7.5g/dl). Immediately before and 10 minutes following transfusion of one single RBC unit, a central venous and an arterial blood sample were taken simultaneously and the following parameters were obtained using a Siemens Rapidpoint 500 blood gas analyzer (Siemens Healthineers, Erlangen, Germany):

- Hemoglobin
- Hematocrit
- Blood lactate
- Carbon dioxide partial pressure (pCO_2)
- Central venous oxygen saturation ($ScvO_2$)

The central venous-to-arterial carbon dioxide difference (dCO_2) was calculated as follows:

$dCO_2 = pCO_2$ (central venous) - pCO_2 (arterial)

Additional data recorded comprised:

- Body weight
- Body height

Body Mass Index (BMI) was calculated using the formula: BMI [kg/m^2] = body weight [kg]/body height [$m]^2$.

Statistical analyses and visualizations were performed using MS Excel 2019 (Microsoft Corp., Redmond, CA, USA) and GraphPad PRISM 8 (La Jolla, CA, USA). Data are presented as median values with interquartile range (25-75) and were analyzed using Mann-Whitney test or Wilcoxon signed rank test, respectively, and Spearman correlation. The alpha level was set to 0.05. A sample size calculation prior to recruiting of the first participant revealed that at least 46 subjects would be required for suffi-

cient power (given an effect size of 40%, a type-I error probability of 0.05 and a power of 85%). All data sets are available from the author upon reasonable request. This investigation did neither unblind any data nor analyze any group differences of the large LIBERAL trial.

Results

In total, 50 patients were prospectively included to participate in the study. Four cases were excluded due to incomplete sampling, resulting in 46 arterial and venous blood samples before and 46 arterial and venous samples after RBC transfusion (184 blood samples in total). Median patient age was 79 (75–83) years. The cohort comprised 46 patients, receiving upper or lower limb surgery in 25 and spine surgery in 21 cases. Median body weight was 76 (64–89) kg, height was 168 (162–178) cm, and Body Mass Index (BMI) was 26.6 (23.7–31.1) kg/m^2.

Baseline median hemoglobin before RBC transfusion was 8.35 (7.48–8.73) g/dl in arterial blood samples (Figure 1), while hematocrit was 24.5 (22–26) %. Blood lactate was 0.97 (0.84-1.38) mmol/l. Median arterial carbon dioxide partial pressure (pCO2) was 40.7 (37-44.6) mmHg. In central venous blood samples, median pCO2 was 47.2(43.6–50.6) mmHg, while oxygen saturation (ScvO2) was 78 (71–82) %. Before transfusion, median dCO2 was 6.2 (3.4-9.6) mmHg. According to Spearman correlation, there was a linear association between pre-transfusion dCO2 and ScvO2, with higher dCO2 values being associated with a lower ScvO2 (r=-0.37, p=0.01). There was no correlation between pre-transfusion hemoglobin and dCO2, ScvO2 or lactate.

Transfusion of one RBC unit resulted in a significant increase of hemoglobin and hematocrit in arterial blood samples (Figure 1), and there was no significant difference between hemoglobin values in arterial and central venous blood. Median hemoglobin increase was 1.2 (0.7–1.63) g/dl, while hematocrit increased by 4 (2–5) %. Accordingly, post-transfusion hemoglobin was 9.4 (8.88–9.83) g/dl (p<0.0001 vs. pre-transfusion), and post-transfusion hematocrit was 28 (26–29)% (p<0.0001). Hemoglobin increase was more pronounced when pre-transfusion hemoglobin was low, as evidenced by a significant negative association between both parameters (r=-0.61, p<0.0001) (Figure 2). The same applied for the hematocrit (r=-0.58, p<0.0001). Neither body weight nor height nor BMI had a significant influence on hemoglobin or hematocrit increase.

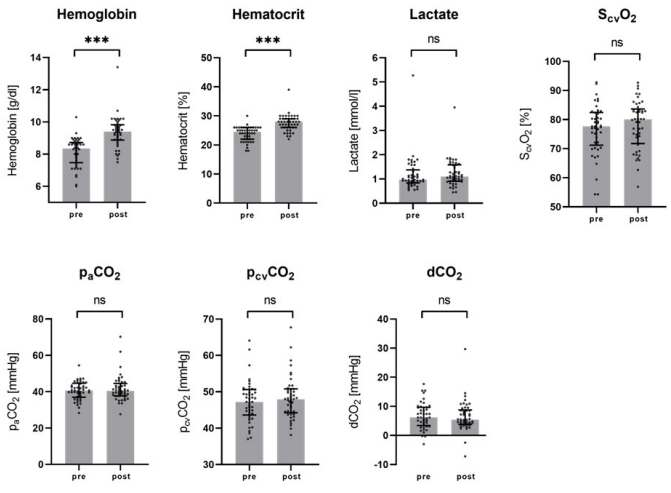

Figure 1: Pre- and post-transfusion values.
In orthopedic and trauma surgery patients, blood was drawn simultaneously from an indwelling radial arterial as well as central venous catheter before (pre) and 10 minutes after transfusion of one red blood cell unit (post). Hemoglobin, hematocrit, lactate, central venous oxygen saturation (ScvO2), arterial and central venous carbon dioxide partial pressure (paCO2, pcvCO2) and the venous-to-arterial carbon dioxide difference (dCO_2) were measured or calculated, respectively.
Data are visualized as bar diagrams and scatter dot plot with median and interquartile range (25-75). n=46. Wilcoxon signed rank test. ***p<0.005

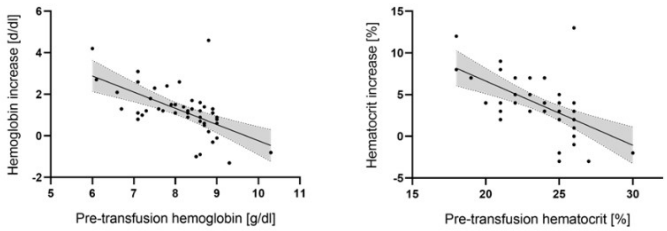

Figure 2: Pre-transfusion values and hemoglobin and hematocrit increase.
Diagrams show the association between pre-transfusion hemoglobin (left) and hematocrit (right) and hemoglobin and hematocrit increase (respectively) following transfusion of one red blood cell unit.
Spearman correlation. Grey area shows 95% confidence band.

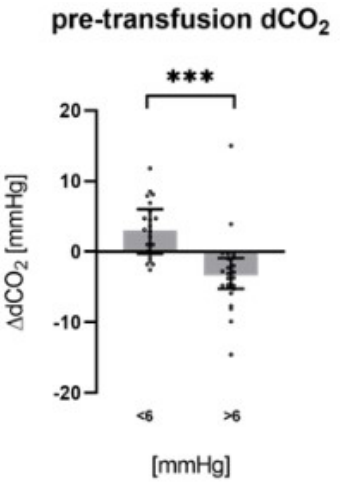

Figure 3: Pre-transfusion dCO_2 and change following transfusion.
The whole cohort was divided according to pre-transfusion dCO_2 values (below or above a cut-off value of 6 mmHg, respectively). Median dCO_2 decreased significantly more pronounced following transfusion when pre-transfusion values were high (>6 mmHg, n=24), compared to those patients with a pre-transfusion dCO_2 below 6 mmHg (n=22).
Mann-Whitney test. ***p<0.005

In contrast to hemoglobin and hematocrit, neither lactate nor $ScvO_2$ nor dCO_2 were significantly influenced by transfusion (median post-transfusion lactate 1.1 (0.91–1.59) mmol/l (p=0.06 vs. pre-transfusion), $ScvO_2$ 80 (72–84) % (p=0.15), dCO_2 5.5 (3.8–8.8) mmHg (p=0.63) (Figure 1). Although not influenced, as before transfusion, again there was a linear negative association between post-transfusion dCO_2 and $ScvO_2$ (r=-0.29, p=0.047). When the whole cohort was divided according to pre-transfusion dCO_2 values (below or above a cut-off value of 6 mmHg, respectively [8]), median dCO_2 decreased significantly more pronounced following RBC transfusion when pre-transfusion values were high (>6 mmHg), compared to those patients with a pre-transfusion dCO_2 below 6 mmHg (p<0.0001, Figure 3). This could not be observed for $ScvO_2$.

Discussion

An increase in the difference between central venous and arterial carbon dioxide partial pressure (dCO_2) has been demon-

strated to be indicative for impaired capillary perfusion. However, despite results from animal studies suggest that severe bleeding alters this parameter, it is still elusive if red blood cell transfusion in humans also has an effect on dCO_2 values. Our results demonstrate that in orthopedic and trauma surgery patients, dCO_2 is inversely associated with $ScvO_2$. Transfusion of one RBC unit significantly increased hemoglobin and hematocrit, and at lower pre-transfusion values, RBC administration had a more pronounced effect on this increase. Neither lactate nor $ScvO_2$ nor dCO_2 were influenced by RBC transfusion. However, median decrease in dCO_2 was significantly more pronounced at pre-transfusion values above 6 mmHg, compared to those below this cut-off.

Human cell metabolism is oxygen-dependent. Glucose is oxidized during aerobic cellular respiration (glycolysis, oxidative decarboxylation, citric acid cycle and oxidative phosphorylation) via various intermediate products (pyruvate, acetyl-CoA, isocitrate, NADH). In the end, the energy transferred is used to generate bonds between Adenosine Diphosphate (ADP) and a further phosphate group to form high-energy Adenosine Triphosphate (ATP). Also, low-energy waste products (water and CO_2) are created during this process. ATP is then used to drive energy-consuming cellular vital processes such as various substeps of DNA, RNA and protein synthesis, intra- and extracellular signaling or enzymatic activity. Therefore, oxygen supply to the cells is crucial.

Usually, in resting state, oxygen delivery to organs and tissues exceeds demand by far. While oxygen consumption in a healthy adult at rest is approximately 200-250 ml/min, delivery to the body achieves 800–1,000 ml/min. Blood returning to the lungs from periphery is still saturated with oxygen to a large extent, illustrating the physiological reserves of this system. A mixed-venous blood sample drawn from the pulmonary artery, showing an oxygen saturation of about 75%, is supposed to be indicative of a physiologically well-balanced relation between oxygen consumption and supply. If this balance is lost (either due to increased oxygen demand or to reduced cardiac output or limited oxygen transport capacity of the blood), this results in an increased peripheral oxygen extraction, evidenced by a reduced mixed-venous saturation [12]. The relevance of a decreased $SmvO_2$ (or $ScvO_2$) to diagnose critically impaired circulation, to evaluate the success of therapeutic measures and also as an outcome-related parameter in critically ill patients is meanwhile well accepted [5,12-15]. This holds especially true for changes over time [16]. Therefore, $ScvO_2$ as well as $SmvO_2$ can also be determined continuously by fiberoptics [12]. Hence, determination of $SmvO_2$ has been implemented into guidelines to treat shock and circulatory failure [17-19]. $ScvO_2$, which is determined via a central venous instead of a (more invasive) pulmonary artery catheter, is supposed to be about 5 % lower than $SmvO_2$ in absolute values, but it compares to the latter in its diagnostic relevance. Again, this particularly holds true for changes, usually occurring equally in $ScvO_2$ as well as $SmvO_2$ [12].

For both parameters, an association with hemoglobin levels has been demonstrated [16]. This relation between cardiac output (Q), hemoglobin (Hgb) and $SmvO_2$ can be derived from the equation: $Q = (VO_2)sys/[13.9 \cdot [Hgb] \cdot (SaO_2 - SmvO_2)]$.

With unchanged cardiac output, a reduction in hemoglobin content results in a decrease in $SmvO_2$. However, clinically, acute hemorrhage or hemodilution has been shown not to affect $SmvO_2$ values until the hemoglobin level falls by approximately 50% because of a compensatory increase in cardiac output [10,20]. Our results are in line with that. Although in the whole cohort, median hemoglobin values were below the normal range given for adults (12-18g/dl), $ScvO_2$ values were not significantly lowered (normal range >70%).

The relation between cardiac output and $SmvO_2$ (and thus also $ScvO_2$) is derived from the principle of Fick. The flow through the body of an indicator substance absorbed or released by the tissue is proportional to the difference of its concentration on the arterial and on the venous side. Similar to oxygen as an indicator that is absorbed by tissue (and measured in the arterial and the returning mixed venous blood), the principle of Fick can also be applied to CO_2 (as an indicator released from tissue into the blood). As described above, CO_2 is produced as waste product of aerobic cellular respiration in the citric acid cycle. Upon release, it is carried via capillaries, venules and the larger veins to the lungs and exhaled. Therefore, the difference between the CO_2 content in venous and in arterial blood is likewise proportional to capillary perfusion. This relation is meanwhile well established: dCO_2 is proportional to CO_2 production and inversely related to cardiac output (and tissue perfusion) [6,7,21]. Clinically, it may therefore serve as a surrogate marker of venous return and the adequacy of cardiac output – for diagnostic and therapeutic approaches as well [6,7,22-24]. A dCO_2 of 6 mmHg is considered a cut-off value - if capillary perfusion decreases to a critical degree, more CO_2 is released into blood per time, causing the dCO_2 to increase to values above 6 mmHg [8]. An association with a worsened outcome in surgery patients has been shown [25]. Since CO_2 is approximately 20 times more soluble in the blood compared to oxygen, an increased dCO_2 can indicate a perfusion mismatch in critically ill patients even when $ScvO_2$ is still within a normal range [7]. In our cohort, $ScvO_2$ and dCO_2 were inversely correlated both before and after transfusion (i.e., increase in hemoglobin). This is in line with the findings of Al Duhailib et al. in a large population of more than 2,000 patients [23].

As expected, both hemoglobin level and hematocrit increased significantly by administration of one RBC unit in our cohort. Interestingly, the lower the pre-transfusion value was, the more pronounced was the increase in hemoglobin. Typically, according to the rule of thumb, transfusion of one unit of RBC in a normally constituted adult is expected to raise hemoglobin by 1g/dL [26]. Factors known to influence this include gender and BMI. In our study population, neither body weight nor height nor BMI had a significant influence on the increase. However, the dependence on pre-transfusion values we observed had already be described by others, e.g., by Naidech et al. in patients with subarachnoid hemorrhage [27]. Similarly, in trauma patients, cerebral oxygenation, which (in part) also depends on hemoglobin levels, is improved by transfusion to a greater extent the more impaired it was before [28]. Others demonstrated similar results for $ScvO_2$, which could be improved by transfusion only in those patients whose pre-transfusion $ScvO_2$ was already reduced and below 70% [29,30]. Hence, patients showing a more markedly compromised tissue oxygenation at decreased hemoglobin levels particularly benefit from transfusion, which highlights the value of an individualized approach to RBC administration, as opposed to fixed hemoglobin threshold values. Of note, in our study cohort, the majority (37 of 46) of pre-transfusion $ScvO_2$ values were above 70% and therefore we did not observe these effects of RBC transfusion on $ScvO_2$.

In our patient cohort, transfusion of one RBC unit had a sig-

nificant effect on hemoglobin and hematocrit, but not on $ScvO_2$ or dCO_2. This may not be unexpected, given the fact that even before transfusion there was no association between hemoglobin and $ScvO_2$ or dCO_2 and that these both parameters (in contrast to hemoglobin) were measured within their normal ranges. Nevertheless, results from animal studies suggest an effect of pathologically decreased hemoglobin level in the setting of severe bleeding on dCO_2. In a study by Kocsi et al., sequential and controlled severe isovolemic anemia was established in Vietnamese mini pigs [10]. A significant decrease in $ScvO_2$ as well as an increase in dCO_2 occurred, but only when hemoglobin levels decreased by more than 50%. This may explain why the (though significant but) only moderate change in hemoglobin levels in our whole cohort (median increase 1.2g/dL, corresponding to about 15% of pre-transfusion values) had no effect on $ScvO_2$ or dCO_2. Similar results were seen by Dubin et al. in a sheep hemorrhage model, who could not observe a change in dCO_2 due to only a moderate reduction of hemoglobin concentration (as long as there was no concomitant reduction in cardiac output) [31,32]. Moreover, our results reflect those of Themelin et al., who studied the effect of RBC transfusion on (normal) dCO_2 values in a cohort of 62 patients and observed no significant changes, achieving similar increases in hemoglobin levels as we did (1.0g/dL) [29].

Interestingly and comparable with the effect of pre-transfusion hemoglobin on the increase following RBC administration, in our study, dCO_2 decreased significantly more pronounced in those patients with a pre-transfusion dCO_2 above the threshold value of 6 mmHg, compared to those below this cut-off. This again suggests that patients with an impaired capillary perfusion at decreased hemoglobin levels (in this case reflected by an elevated dCO_2) may benefit more from RBC transfusion than those with normal pre-transfusion values.

It should be assumed that for a more restrictive and individualized approach, in addition to a decreased hemoglobin value, parameters of impaired oxygenation or capillary perfusion mismatch should be taken into account when considering administering RBC. This may have the potential to reduce transfusion incidence without a negative impact on patient outcome [33]. Reasonable parameters can be $ScvO_2$ or markers of cerebral oxygenation, as described above, but also, as in our case, increased dCO_2 [28-30,34]. In fact, the protocol of a prospective cohort study to systematically investigate the value of dCO_2 in combination with parameters of tissue oxygenation as transfusion trigger was recently published [35]. Its results as well as those of the ongoing LIBERAL trial may be helpful towards the development of more individualized transfusion approaches [11].

Our study has some limitations. First (and most significant), neither cardiac output nor microcirculation itself have been monitored directly. An upcoming study involving sublingual sidestream dark field imaging to evaluate our herein presented results should gain further insights on the relationship between transfusion outcome, dCO_2 and capillary tissue perfusion. Second, sample size of our cohort was restricted, and our study population did not comprise critically ill patients with more severely impaired circulation. Therefore, our results may not necessarily be transferred to other patient populations and should be interpreted as pilot results that have to be validated in a larger trial.

In summary, the results of our study suggest that crude dCO_2 is not influenced by moderate hemoglobin increases in orthopedic and trauma surgery patients. However, including dCO_2 into the decision whether to administer RBC or not may be an interesting approach for further investigations on the way towards more individualized transfusion regimens.

Author Statements

Ethics Approval and Consent to Participate

The leading ethics committee (University Wuerzburg 87/17_ff) and local ethics committee (University Hospital Bonn, Germany; protocol number 096/17-AMG) considered the study (clinical trials: NCT03369210) to be compliant with the applicable professional codes and regulations and thereby approved the study protocol. All patients provided written informed consent prior to inclusion into the study.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Conflicts of Interest

The authors state that they have no conflicts of interest to declare.

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